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Highly Enantioselective Regiodivergent and Catalytic Parallel Kinetic Resolution

Fabio Bertozzi, Paolo Crotti, Franco Macchia, Mauro Pineschi* Ben L. Feringa*

General methods. All reactions were conducted in flame dried glassware with magnetic stirring under an atmosphere of argon. Toluene and diethyl ether were distilled from sodium/benzophenone ketyl and stored under argon. Et₂Zn (1.1 M solution in toluene) and Me₂Zn (2.0 M solution in toluene) were purchased from Aldrich. Analytical TLC were performed on Alugram SIL G/UV254 silica gel sheets (Macherey-Nagel) with detection by 0.5% phosphomolybdic acid solution in 95% EtOH. Silica gel 60 (Macherey-Nagel 230-400 mesh) was used for flash chromatography. Solvents for extraction and chromatography were HPLC grade.

Optical rotation were measured on a Perkin-Elmer 241 digital polarimeter with a 1 dm cell. ¹H NMR spectra were recorded on a Bruker AC-200 spectrometer on CDCl₃ solution. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuteriochloroform: δ 7.26). ¹³C NMR spectra were recorded on a Bruker AC-200 (50 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuteriochloroform: δ 77.7). Gas chromatography was performed on a Perkin-Elmer 8420 apparatus (FI detector) using a Chromopak fused silica 50 m x 0.25 mm column, coated with CP-Cyclodextrin-B-236-M-19). In all cases, the injector and detector temperature was 250°C and a 0.9 mL / min helium flow was employed.

General procedure for the regiodivergent parallel kinetic resolution. A solution of Cu(OTf)₂ (10.83 mg, 0.030 mmol) and (*R,R,R*)-**1** (32.3 mg, 0.06 mmol) in anhydrous toluene (4.0 mL) was stirred at r.t. for 40 min. The colorless solution was cooled to -78 °C, and subsequently additioned with a solution of racemic vinyloepoxide (2.0 mmol) in toluene (1.0 mL) and with 3.0 mmol of R₂Zn (solution in toluene). The resulting light yellow solution was quenched with saturated aqueous NH₄Cl (5.0 mL) once the reaction reached completion (GC analysis). Extraction with Et₂O and evaporation of the dried (MgSO₄) organic phase gave the crude product, which was subjected to flash chromatography.

***R*-(+)-3-Propyl-2-cyclohexen-1-ol (**3a**):¹**

The general procedure was followed employing 220 mg of racemic vinyloxirane **2**² (2.0 mmol), Cu(OTf)₂ (10.8 mg, 0.03 mmol), chiral ligand (*R,R,R*)-**1** (32.3 mg, 0.06 mmol) and Et₂Zn (2.72 mL, 3.0 mmol). The usual work-up afforded a crude reaction mixture which was subjected to flash chromatography (SiO₂) with 10% EtOAc: hexanes to give 129 mg of pure **3a** (46%), as a liquid. TLC (15% EtOAc/hexanes) R_f=0.14. [α]_D=+43 (c=1.0, CHCl₃).

The enantiomeric excess of **3a** (80%) was determined by chiral GC (CP-cyclodex-β-column), isothermal 110°C, *S*-(-) (minor) t_R30.78 min, *R*-(+) (major) t_R 31.72 min.

(1*S*, 2*S*)-(-)-3-Methylidene-2-ethyl-1-cyclohexanol (4a**):**

The first eluting fractions of the above described flash chromatography afforded 104 mg of pure **4a** (37%) as a liquid. TLC (15% EtOAc/hexanes) R_f=0.20. [α]_D=-8.9 (c=1.12, CHCl₃).

¹H NMR δ 4.84 (bs, 1H, methylidene **H**), 4.73 (bs, 1H, methylidene **H**), 3.65-3.72 (m, 1H, CH-OH), 1.95-2.21 (m, 3H, allylic-**H**), 1.38-1.85 (m, 6H, -CH₂-), 0.87 (t, 3H, -CH₃, *J*=7.3 Hz).

¹³C NMR δ 178.53, 111.60, 73.08, 54.16, 32.53, 30.39, 23.46, 23.32, 12.66.

Anal. Calcd. for $C_9H_{16}O$: C, 77.08; H, 11.51. Found : C, 77.24; H, 11.38.

The enantiomeric excess of **3a** (99%) was determined by chiral GC (CP-cyclodex- β -column), isothermal 110 °C, (1*R*, 2*R*)-(+ (minor) t_R 23.44 min, (1*S*, 2*S*)-(-) (major) t_R 23.87 min.

(*R*)-(+)-3-Ethyl-2-cyclohexen-1-ol (3b):³

The general procedure was followed employing 110 mg of racemic vinyloxirane **2** (1.0 mmol), $Cu(OTf)_2$ (5.4 mg, 0.015 mmol), chiral ligand (*R,R,R*)-**1** (16.2 mg, 0.03 mmol) and Me_2Zn (0.75 mL, 1.5 mmol). The usual work-up afforded a crude reaction mixture which was subjected to flash chromatography (SiO_2) with 10% EtOAc: hexanes to give 51 mg of pure **3b** (40%), as a liquid. TLC (20% EtOAc/hexanes) R_f =0.21.

The enantiomeric excess of **3b** (96%) was determined by chiral GC (CP-cyclodex- β -column), isothermal 115 °C, (*S*)-(-) (minor) t_R 35.21 min, (*R*)-(+ (major) t_R 35.67 min.

(1*S*, 2*S*)-(+)-3-Methylidene-2-methyl-1-cyclohexanol (4b):

The first eluting fractions of the above described flash chromatography afforded 47 mg of pure **4b** (37%) as a liquid. TLC (20% EtOAc/hexanes) R_f =0.29. $[\alpha]_D^{+27}$ (c =0.53, $CHCl_3$). 1H NMR δ 4.78 (bs, 1H, methylidene-**H**), 4.69 (bs, 1H, methylidene-**H**), 3.23 (dt, 1H, -**CHOH**, J =3.9 and 8.8 Hz), 2.19-2.35 (m, 1H, -**CHCH**₃), 1.86-2.14 (m, 3H), 1.68-1.83 (m, 1H), 1.31-1.53 (m, 2H), 1.16 (d, 3H, -**CH**₃, J =6.8 Hz).

^{13}C NMR δ 151.30, 108.45, 76.59, 46.30, 35.41, 34.57, 25.22, 15.17.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found : C, 76.29; H, 11.35.

The enantiomeric excess of **4b** (92%) was determined by chiral GC (CP-cyclodex- β -column), isothermal 105 °C, (1*R*, 2*R*)-(-) (minor) t_R 27.72 min, (1*S*, 2*S*)-(+ (major) t_R 28.14 min.

(1R, 4R)-(+)-4-Ethyl-2-cyclohexen-1-ol (6a):

The general procedure was followed employing 96 mg of racemic vinyloxirane **5**⁴ (1.0 mmol), Cu(OTf)₂ (5.40 mg, 0.015 mmol), chiral ligand (*R,R,R*)-**1** (16.2 mg, 0.03 mmol) and Et₂Zn (1.36 mL, 1.5 mmol). The usual work-up afforded a crude reaction mixture which was subjected to flash chromatography (SiO₂) with 20% EtOAc: hexanes to give 78 mg of pure **6a** (62%) as a liquid.

¹H NMR δ 5.58-5.72 (m, 2H, olefinic-**H**), 4.32-4.36 (m, 1H, -**CHOH**), 1.75-2.13 (m, 3H), 1.08-1.47 (m, 4H, -**CH**₂-), 0.88 (t, 3H, -CH₂**CH**₃, *J*=7.3 Hz).

¹³C NMR δ 135.01, 130.97, 67.75, 37.61, 32.64, 29.26, 27.10, 11.93.

Anal. Calcd. for C₈H₁₄O: C, 76.14; H, 11.18. Found : C, 76.35; H, 11.24.

The enantiomeric excess of **6a** (34%) was determined by chiral GC (CP-cyclodex-β-column), isothermal 115 °C, (1*S*, 4*S*)-(-) (minor) *t*_R25.98 min, (1*R*, 4*R*)-(+)-(major) *t*_R 26.78 min.

(1S, 2S)-(+)-2-Ethyl-3-cyclohexen-1-ol (7a):

The first eluting fractions of the above described flash chromatography afforded 18 mg of pure **7a** (14%) as a liquid. [α]_D=+97.4 (*c*=1.5, CHCl₃).

¹H NMR δ 5.59-5.71 (m, 1H, olefinic-**H**), 5.47-5.56 (m, 1H, olefinic-**H**), 3.53-3.67 (m, 1H, -**CHOH**), 1.77-2.16 (m, 4H), 1.24-1.74 (m, 3H), 0.94 (t, 3H, -CH₂**CH**₃, *J*=7.3 Hz).

¹³C NMR δ 129.29, 127.12, 71.39, 45.92, 30.61, 26.14, 24.43, 11.55.

Anal. Calcd. for C₈H₁₄O: C, 76.14; H, 11.18. Found : C, 76.30; H, 11.32.

The enantiomeric excess of **7a** (>98%) was determined by chiral GC (CP-cyclodex-β-column), isothermal 110 °C, (1*S*, 2*S*)-(+)(major) *t*_R24.06 min, (1*R* 2*R*)-(-) (minor) *t*_R 24.56 min.

(1*R*, 4*R*)-(+) -4-Methyl-2-cyclohexen-1-ol (6b):⁵

The general procedure was followed employing 192 mg of racemic vinyloxirane **5** (2.0 mmol), Cu(OTf)₂ (10.8 mg, 0.03 mmol), chiral ligand (*R,R,R*)-**1** (32.3 mg, 0.06 mmol) and Et₂Zn (2.72 mL, 3.0 mmol). The usual work-up afforded a crude reaction mixture which was repeatedly⁶ subjected to flash chromatography (SiO₂) with 10% EtOAc: hexanes to give 85 mg of pure **6b** (38%) as a liquid.

The enantiomeric excess of **6b** (64%) was determined by chiral GC (CP-cyclodex-β-column), isothermal 104 °C, (1*S*,4*S*)-(-) (minor) *t*_R19.94 min, (1*R*, 4*R*)-(+) (major) *t*_R 20.72 min.

(1*S*, 2*S*)-(+) -2-Methyl-3-cyclohexen-1-ol (7b):⁷

The first eluting fractions of the above described flash chromatography afforded a total amount of 45 mg of pure **7b** (20%) as a liquid.

The enantiomeric excess of **7b** (>97%) was determined by chiral GC (CP-cyclodex-β-column), isothermal 104 °C, (1*S*, 2*S*)-(+) (major) *t*_R19.73 min, (1*R*, 2*R*)-(-) (minor) *t*_R 20.46 min.

Determination of Absolute Configurations of 7b:

To a 60:40 mixture of **6b** and **7b** (80 mg) in absolute EtOH (7 mL) was added a catalytic amount of Pd on charcoal. The resulting mixture was vigorously stirred overnight under a H₂ atmosphere at rt. Filtration through a pad of Celite^R and evaporation of the organic solvent afforded a crude reaction mixture which was subjected to flash chromatography (SiO₂) with 13% EtOAc: hexanes to give 5 mg of pure (1*S*, 2*S*)-(+) -2-methylcyclohexanol.⁸

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